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Non-invasive measurement of left ventricular function in coronary artery disease

*Comparison of first pass radionuclide ventriculography, M-mode echocardiography, and systolic time intervals**

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SUMMARY Fifty consecutive patients having had cardiac catheterisation for coronary artery disease also underwent testing by three non-invasive methods commonly employed for assessment of left ventricular function. These included the first pass radionuclide ejection fraction, fractional shortening of the M-mode echocardiographic left ventricular internal dimension, and pre-ejection period/left ventricular ejection time ratio derived from systolic time intervals (PEP/LVET). Linear correlations of these non-invasive measures with cineangiographic ejection fractions were calculated. The first pass radionuclide ejection fraction correlated best. Echocardiograms and systolic time intervals proved less versatile since 11 of 50 echocardiograms were technically not suitable for measurement and 11 of 50 systolic time intervals could not be used because of left ventricular conduction delays. Overall, radionuclide ventriculography proved to be the most accurate and practical of these non-invasive techniques in evaluating left ventricular function in this group of patients with coronary artery disease.

Among measures of left ventricular performance, the cineangiographic ejection fraction has been shown to be the single most important prognostic index in patients with coronary artery disease.[1–5] Non-invasive methods for estimating this information have obvious appeal and have become increasingly popular. Within the past decade, systolic time intervals,[6–10] echocardiography,[11–17] and, more recently, radionuclide techniques[18–24] have been used to assess myocardial performance. Each of these methods has been examined individually and compared with results of left ventricular cineangiography but the comparative merits and limitations of different non-invasive tests of left ventricular function have not received a great deal of attention. This study was designed to identify which of the above commonly available non-invasive methods is the most accurate and versatile procedure in assessing left ventricular function relative to cineangiography in an unselected group of patients with coronary artery disease.

Methods

Fifty consecutive male patients, ages 32 to 63, with coronary artery disease and without significant valvular heart disease were entered in the study. Each patient had the following tests performed: (1) a standard 12 lead scalar electrocardiogram recorded on the morning before cineangiographic study; (2) an echocardiogram, carotid pulse tracing, and phonocardiogram recorded within four days of cardiac catheterisation; (3) a first pass technetium-99m pertechnetate left ventricular study completed during the period in hospital; (4) a left ventricular cineangiogram at cardiac catheterisation. The non-invasive studies were reviewed by observers who did not know the results of the left ventricular cineangiogram.

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ECHOCARDIOGRAPHIC EVALUATION

Echocardiographic strip chart recordings were made on an Irex Cardiac Ultrasound Module 150-149 interfaced with an Irex Continue-Trace, 101 multichannel photographic recorder. An Aerotech 1·6 or 2·25 MHz uncollimated transducer was employed with the patient either supine or in the left lateral decubitus position. Echocardiographic left ventricular dimensions were determined just below the mitral leaflets. Only those recordings with well-defined left ventricular endocardium along the interventricular septum and posterior wall were included. Left ventricular internal dimensions were measured at end-diastole (LVIDd) and at end-systole (LVIDs) (Fig. 1A). End-diastole was chosen at the onset of the QRS complex. End-systole was chosen as the time of the peak of the most anterior motion of the left ventricular posterior wall. Internal dimensions were measured from the leading edge of the left side of the septal endocardium to the leading edge of the endocardium of the left ventricular posterior wall. From these measurements, fractional shortening (FS) was calculated.

$$FS = \frac{LVIDd - LVIDs}{LVIDd}$$

SYSTOLIC TIME INTERVAL EVALUATION

Carotid pulse tracing and phonocardiogram recordings were made with the same Irex Cardiac Ultrasound Module. An Irex pulse transducer with funnel and a Cambridge phonocardiographic microphone head were used. Patients with intraventricular conduction delay (QRS duration >0·10 s) were excluded. Measurements included

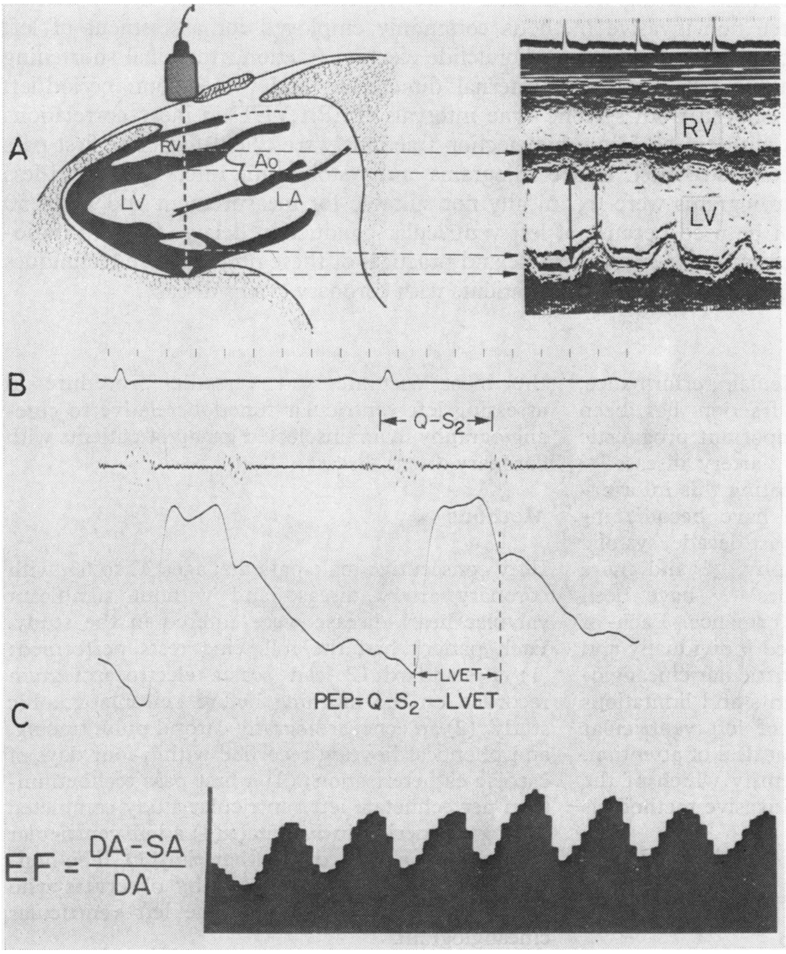

Fig. 1 *Methods.* (A) *M-mode echocardiography.* Left: *schematic long axis view of the heart showing path of ultrasonic beam from transducer placed parasternally on chest wall.* Right: *echocardiogram showing ventricular internal dimensions changing with time. Left ventricular internal diastolic dimension is shown by large arrowed line and systolic dimension by small arrowed line. RV, right ventricle; LV, left ventricle; LA, left atrium; Ao, aorta.* (B) *Systolic time intervals. Electrocardiogram is at top, with simultaneous phonocardiogram (middle) and carotid pulse trace (bottom).* $Q\text{-}S_2$*=electrocardiogram Q wave to second heart sound interval; LVET, left ventricular ejection time; PEP, pre-ejection period.* (C) *Radionuclide flow study. Time activity histogram from left ventricular region of interest. The peaks represent diastolic activity (DA) and troughs systolic activity (SA) during passage of the radionuclide through the left ventricle. The ejection fraction (EF) is determined from the formula to the left of the histogram.*

Q-S_2 (the time from initial onset of QRS to the first high frequency component of the second heart sound) and left ventricular ejection time (LVET—the time from onset of initial rapid rise of carotid pulse to the trough of the incisura). The pre-ejection period (PEP) was calculated by subtracting LVET from the Q-S_2 (Fig. 1B). The ratio of PEP/LVET was determined from five successive beats in each subject.

RADIONUCLIDE EVALUATION

Cardiac imaging was accomplished during the first transit of a 15 mCi bolus of technetium-99m rapidly injected in an antecubital vein. With a multicrystal scintillation camera (Baird Atomic System 77) directed at 45° left anterior oblique with a 20° caudal tilt a left ventricular region of interest was defined and a time radioactivity histogram was constructed during the passage of the bolus through the left ventricle (Fig. 1C). The beats with maximum activity (usually four or five in number) were selected and corrected for background activity by subtracting the activity measured over the left ventricular region of interest immediately before radionuclide entry.

The sums of background corrected activities during diastole (DA) and systole (SA) were used to calculate ejection fraction (EF) as follows:

$$EF = \frac{DA - SA}{DA}$$

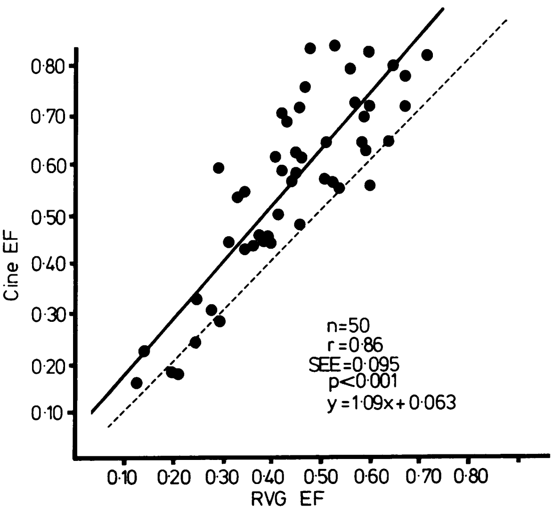

Fig. 2 *Relation of radionuclide ventriculogram ejection fraction (RVG EF) to cineangiographic ejection fraction (Cine EF) in 50 patients. r, correlation coefficient; SEE, standard error of the estimate.*

LEFT VENTRICULAR ANGIOGRAPHY EVALUATION

Retrograde left heart catheterisation was performed using either a brachial or femoral approach. Left ventricular cineangiograms were filmed at 60 frames/s on 35 mm film using a 9-inch image intensifier in the 30° RAO position; 40 to 60 ml of 76 per cent meglumine and sodium diatrizoate

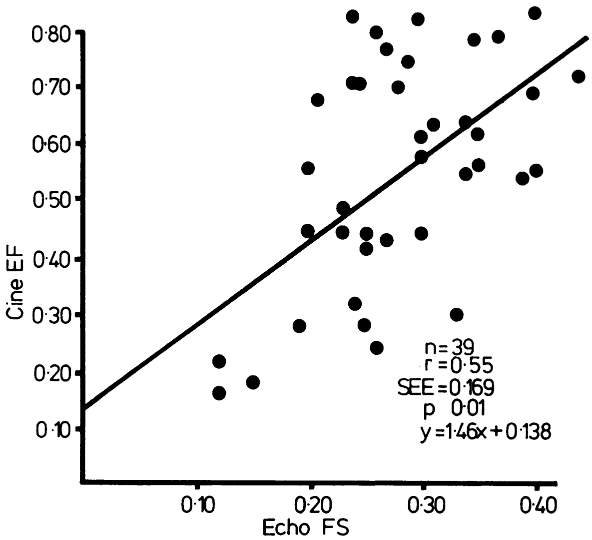

Fig. 3 *Relation of electrocardiographic fractional shortening (Echo FS) to cineangiographic ejection fraction (Cine EF) in 39 patients. Abbreviations as in Fig. 2.*

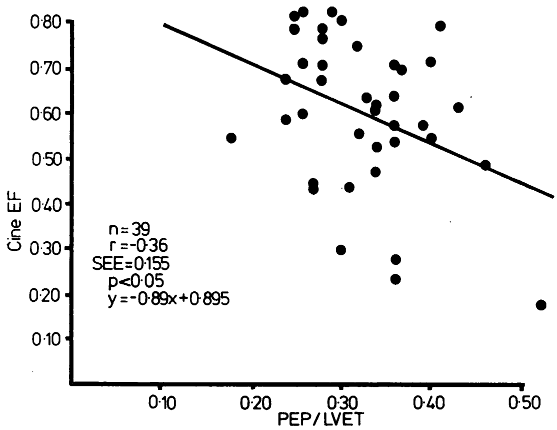

Fig. 4 *Relation of pre-ejection period to left ventricular ejection time ratio (PEP/LVET) to cineangiographic ejection fraction (Cine EF) in 39 patients. Other abbreviations as in Fig. 2.*

(Renografin 76) were injected over three to four seconds. Quantitative ventriculography was performed using the single plane area length method of Kennedy *et al.*[25] derived from the biplane method of Dodge *et al.*[26]

STATISTICAL CONSIDERATIONS

The results of each non-invasive method were compared with cineangiographic ejection fraction using standard linear regression formulae and a Monroe 325 programmable calculator.

Results

The Table displays all pertinent data. All patients had successful radionuclide ventriculography. Eleven patients had technically inadequate echocardiograms and 11 patients did not qualify for systolic time intervals because of the presence of left ventricular conduction defects. Since one patient (case 11) was common to both groups, 29 patients were successfully evaluated by all three non-invasive techniques. Fig. 2, 3, and 4 show the

Table *Summary of patient data*

Case no.	*Age (y)*	*Electrocardiographic myocardial infarction*	*Ejection fraction*		*Echocardiographic fractional shortening*	*PEP/LVET*
			Cine	*Right ventriculography*		
1	60	Anterior	0·64	0·59	0·34	0·33
2	62	Inferior	0·56	0·45	0·20	IVCD
3	55	—	0·22	0·14	0·21	LBBB
4	59	—	0·58	0·46	TI	0·36
5	59	Anterior	0·62	0·46	TI	0·43
6	44	Anterior	0·44	0·39	TI	0·27
7	54	—	0·71	0·68	0·24	0·28
8	49	—	0·72	0·58	0·44	0·40
9	57	—	0·79	0·57	0·35	0·25
10	41	Anterior Inferior	0·18	0·20	0·19	0·52
11	56	—	0·56	0·53	TI	LBBB
12	55	—	0·82	0·61	0·30	0·25
13	51	—	0·81	0·73	TI	0·30
14	60	—	0·53	0·34	TI	0·34
15	59	—	0·83	0·54	0·40	0·26
16	57	—	0·71	0·46	0·24	0·36
17	45	—	0·75	0·48	0·29	0·32
18	56	—	0·55	0·54	0·40	0·18
19	62	—	0·58	0·43	0·30	0·39
20	53	Anterior	0·43	0·37	0·27	IVCD
21	46	Inferoposterior	0·71	0·61	TI	0·26
22	50	Anterior	0·16	0·14	0·12	IVCD
23	49	—	0·30	0·28	0·33	0·30
24	60	Inferior Anterior	0·24	0·25	0·26	0·36
25	53	—	0·55	0·61	0·34	0·40
26	45	—	0·64	0·65	TI	0·36
27	58	—	0·56	0·52	0·35	0·32
28	44	—	0·54	0·35	0·38	0·36
29	53	—	0·42	0·35	0·25	LBBB
30	57	Inferior	0·44	0·32	0·25	IVCD
31	44	Inferior	0·45	0·40	0·23	IVCD
32	39	Anterior	0·64	0·52	0·31	LBBB
33	49	—	0·83	0·49	0·24	0·29
34	63	Inferior	0·32	0·25	0·24	IVCD
35	54	—	0·18	0·21	0·15	LBBB
36	62	—	0·69	0·60	0·40	0·28
37	55	—	0·61	0·47	0·30	0·34
38	60	—	0·77	0·68	0·27	0·28
39	51	Anteroseptal	0·47	0·46	TI	0·34
40	46	—	0·80	0·56	0·26	0·41
41	51	—	0·44	0·39	0·30	0·31
42	43	Inferior Anterior	0·61	0·41	TI	0·26
43	46	—	0·79	0·66	0·37	0·28
44	50	—	0·70	0·43	0·28	0·37
45	47	Inferoposterior	0·45	0·38	0·20	0·24
46	60	Inferior	0·68	0·54	0·21	0·24
47	63	—	0·59	0·30	TI	0·24
48	32	—	0·62	0·60	0·35	0·34
49	50	Inferior	0·28	0·30	0·25	0·36
50	54	Inferior	0·49	0·42	0·23	0·46

TI, technically inadequate; LBBB, left bundle-branch block; IVCD, intraventricular conduction defect.

results of linear correlation analysis for each non-invasive test compared with left ventricular cineangiographic ejection fraction. Radionuclide ventriculography ejection fraction correlated best with cineangiographic ejection fraction ($r = 0{\cdot}86$, $p < 0{\cdot}001$) compared with echocardiographic fractional shortening ($r = 0{\cdot}55$, $p < 0{\cdot}01$) and the systolic time interval ratio PEP/LVET ($r = -0{\cdot}36$, $p < 0{\cdot}05$). If only those 29 patients in whom all three tests were technically feasible are considered, radionuclide ventriculography ejection fraction vs. cineangiographic ejection fraction still correlates best ($r = 0{\cdot}82$) compared with echocardiographic fractional shortening vs. cineangiographic ejection fraction ($r = 0{\cdot}29$) and PEP/LVET vs. cineangiographic ejection fraction ($r = -0{\cdot}40$).

Since segmental wall abnormalities may mislead interpretation of left ventricular performance by M-mode echocardiogram, subsets of the population were examined to determine if transmural myocardial infarction affected echocardiographic interpretation. Nineteen patients proved to have electrocardiographic evidence of transmural myocardial infarction (Table). When these were excluded there was no improvement in correlation of echocardiographic fractional shortening with the cineangiographic ejection fraction ($r = 0{\cdot}35$).

Echocardiographic fractional shortening and systolic time intervals were less versatile compared with radionuclide ventriculography since 11 of 50 echocardiograms were technically not suitable for measurement and 11 of 50 systolic time intervals could not be used because of left ventricular conduction delays.

Discussion

Cineangiographic ejection fraction has been shown to be an important index of left ventricular function. Patients with subnormal ejection fractions have a poorer prognosis whether treated medically or surgically. Patients with very poor ejection fraction ($< 0{\cdot}30$) are at proven high risk for revascularisation surgery.[4] If one could identify by non-invasive techniques those patients who were at excessive risk for revascularisation surgery because of low ejection fraction, one could spare the patient the risk and discomfort of cineangiography.

Overall, radionuclide ventriculography proved to be the best non-invasive predictor of cineangiographic ejection fraction. The correlation of radionuclide ventriculography ejection fraction with cineangiographic ejection fraction is consistent with the results of several other studies.[18 20–24] Interestingly, the ejection fraction determined by radionuclide techniques was systematically less than the cineangiographic ejection fraction (Fig. 2). Explanations for this are: (1) the patient may be under stress during cardiac catheterisation and the increased ejection fraction may be the result of circulating catecholamines; (2) planimetry of the cineangiographic outline may underestimate left ventricular end-systolic size by not including a sufficient amount of papillary muscle and trabeculae: (3) the absolute value of the radionuclide ventriculography ejection fraction can be systematically influenced by arbitrarily determined factors in image processing such as background subtraction.

Conceptually, the radionuclide technique offers an advantage since emission counting relates directly to underlying volume. Abnormal ventricular shape would not change the accuracy of this determination. Quantitative cineangiography is based on the assumption that the left ventricle assumes the shape of a prolate ellipse. A diseased ventricle can vary considerably from this model. Therefore, in some patients the cineangiogram may be less accurate than the radionuclide technique in measuring ejection fraction. If so, the correlation between the cineangiographic ejection fraction and the radionuclide ventriculography ejection fraction might have been even closer using biplane cineangiography which provides a more accurate estimation of ventricular volume, but because of practical constraints our cineangiographic studies were limited to a single right anterior oblique plane.

Echocardiographic fractional shortening proved to be less reliable in estimating cineangiographic ejection fraction. Though significant ($p < 0{\cdot}01$), our r value of 0·55 is slightly lower than other authors.[14 15] Echocardiographic determination of left ventricular performance may be inaccurate in those patients with segmental wall abnormalities. The unidimensional view of the left ventricular myocardium by echocardiogram may grossly overestimate (by evaluating hypercontractile segments) or underestimate (by evaluating poorly contractile segments) left ventricular function in patients with coronary artery disease. Since a significant number of coronary artery disease patients have segmental wall abnormalities, we attempted to identify those patients in whom the echocardiographic evaluation of fractional shortening may be inaccurate. Using an electrocardiographic diagnosis of previous transmural myocardial infarction, we were unable to improve correlation of fractional shortening by excluding those patients with evidence of a prior myocardial infarct. The elimination of the 19 patients with electrocardiographic evidence of infarction left a group with a narrow range of ejection fractions, mainly normal, and this lack of variability precluded a high degree of correlation.

This finding is consistent with observations that electrocardiographic evidence of infarction identifies patients with poorer ejection fractions.[27 28]

The use of two-dimensional sector scanning in echocardiography overcomes some of the M-mode limitations discussed above. A correlation coefficient of 0·55 (echo derived ejection fraction vs. cineangiographic ejection fraction) resulted when a series of 35 patients was studied by two-dimensional echocardiography and the ejection fraction was determined using only one dimension (M-mode equivalent) of data. The correlation coefficient improved to 0·78 when the second dimension of data was included in the ejection fraction determination. In this same series of 35 patients first pass radionuclide ventriculography still produced the best correlation with cine ejection fraction ($r = 0{\cdot}88$).[29] Two-dimensional echocardiography was not used in the present study because we wished to compare established techniques which are more immediately available to the clinician.

Systolic time intervals correlated poorly with the cineangiographic ejection fraction. Garrard *et al.*[7] have previously shown very close correlation ($r = -0{\cdot}90$) in a mixed population of patients with both valvular and non-valvular cardiac disease. Weissler[30] reported a correlation of $r = -0{\cdot}85$ in 80 patients with coronary artery disease, the majority of whom were receiving digoxin. Over half the patients in their study populations had significantly abnormal PEP/LVET ($>0{\cdot}40$) as compared with only four of 39 (10%) of our group. A large preponderance of patients with severe left ventricular dysfunction probably explains the closer correlation they obtained with cineangiographic ejection fractions. In a recent report relating PEP/LVET to cineangiographic ejection fractions in 306 patients with ischaemic heart disease Eddleman *et al*.[31] also found a low correlation coefficient ($r = -0{\cdot}55$) with a wide scatter of data points.

The ability to predict, by non-invasive techniques, those patients who have extremely poor ejection fractions was as follows. All patients with cineangiographic ejection fractions $\leqslant 0{\cdot}30$ had radionuclide ventriculography ejection fractions $\leqslant 0{\cdot}30$ (100% sensitivity). Two patients, however, with radionuclide ventriculography ejection fractions $\leqslant 0{\cdot}30$ had cineangiographic ejection fractions of 0·32 and 0·59 (95% specificity). Similar analysis of echocardiographic fractional shortening and PEP/LVET as predictors of cineangiographic ejection fractions $\leqslant 0{\cdot}30$ is problematical because of the wide scatter of data and small number of severely abnormal tests in this unselected population. Using a normal limit of echocardiographic fractional shortening $>0{\cdot}30$ a value of $\leqslant 0{\cdot}30$ identifies six of seven patients whose cineangiographic ejection fraction is $\leqslant 0{\cdot}30$ (86% sensitivity). This cut-off, however, produces 20 false positive tests and correctly identifies only 12 patients with cineangiographic ejection fractions $>0{\cdot}30$ (38% specificity). If a more stringent "normal" limit of $>0{\cdot}20$ is used, sensitivity falls to 43 per cent and specificity rises to 94 per cent. Likewise, sensitivity and specificity of PEP/LVET relative to cineangiographic ejection fraction of 0·30 depends upon the cut-off limit chosen. The commonly quoted normal limit of PEP/LVET is $\leqslant 0{\cdot}44$.[32] Only two of our patients exceeded that limit and one of those was falsely positive (case 50, cine ejection fraction $= 0{\cdot}49$). Hence, only one of four patients with a cine ejection fraction $\leqslant 0{\cdot}30$ is correctly identified (25% sensitivity) though 34 of 35 patients with values above 0·30 are correctly identified (97% specificity).

The ability to obtain satisfactory test results is an important consideration when examining non-invasive methods. All patients had adequate radionuclide ventriculograms but 22 per cent had echocardiograms that were not technically suitable for measurement and 22 per cent had left ventricular conduction delays on their electrocardiograms, precluding the use of systolic time intervals. As a result, radionuclide ventriculography was the most versatile non-invasive method for estimating left ventricular ejection fraction.

In conclusion, radionuclide ventriculography is the most accurate of the non-invasive measures examined for estimating cineangiographic left ventricular ejection fraction. It is very sensitive in discerning patients with poor left ventricular ejection fraction (cine ejection fraction $\leqslant 0{\cdot}30$) and is not limited by the technical problems of echocardiography and the conduction problems of systolic time intervals.

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